REMARKS

In view of the following remarks, the Examiner is requested to reconsider and allow Claims 1-2, 5-7, 10-11, 14-18, 24-30 and 32-40, the only claims pending and under examination in this application.

Formal Matters

Claims 1, 6, 10, 11, 24, 27, 28, 32, 34, 38 and 40 are amended.

Claims 1, 6, 11, 24, 28 and 34 are amended to include the subject matter previously recited in Claim 38, i.e., "at least one symptom is ameliorated for a period of 1 week or longer." Accordingly, dependent Claim 38 is amended herein to recite "at least one symptom is ameliorated for a period of 3 weeks or longer," support for which is found in the experimental section at page 9, line 19.

Claims 1, 10, 11, 24, 27, 28, 32 and 40 are amended for clarity and to correct minor issues of antecedence and dependency.

As these amendments introduce no new matter, their entry by the Examiner is respectfully requested.

Claim Rejection under 35 U.S.C. § 112 second paragraph

The Examiner rejected Claim 10 as being indefinite under 35 U.S.C. § 112 second paragraph for reciting the term "said symptom" with insufficient antecedent basis. Applicants believe that the amendment to Claim 10 presented herein adequately addresses this rejection.

Claim Rejection under 35 U.S.C. § 103

Claims 1-2, 5-7, 10-11, 14-18, 24-30 and 32-40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bockow (U.S. Patent No. 5,709,855) in view of Edwards (U.S. Patent No. 5,989,559), Herbert *et al.* (American J. of Industrial Medicine 37: 62-74, 2000), Hirano *et al.* (U.S. Patent No. 5,869,087), Liebschutz *et al.* (WO 02/22109) and the Applicants' specification. Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, 1, 6, 10, 11, 24, 27,

28, 32, 34, 38 and 40 are amended. To the extent that this rejection applies to the amended claims, it is respectfully traversed.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added . As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The Applicants submit that the Examiner has not established a *prima facie* case of obviousness because: 1) the combined teaching of the cited references does not teach or suggest all the elements of the claimed method; and 2) one of ordinary skill in the art would not predict success in practicing the claimed method, as is discussed in detail below.

1) Not all elements taught or suggested by the cited references

Present Claim 1 recites:

> A method for at least ameliorating a symptom associated with pressure applied to the median nerve of the carpal tunnel of a host, said method comprising:
> topically applying an effective amount of a topical patch NSAID formulation consisting of:
> an adhesive matrix;
> an NSAID dissolved in said adhesive matrix; and
> a backing;
> to a palmar dermal surface of said host proximal to said carpal tunnel;
> to ameliorate at least one symptom associated with pressure applied to the

median nerve of the carpal tunnel of said host;

wherein said at least one symptom is ameliorated for a period of 1 week or longer following application of said topical patch NSAID formulation.

The claimed method is drawn to the amelioration of symptoms associated with pressure applied to the median nerve of the carpal tunnel of a host. An element of the claimed method is that at least one symptom is ameliorated for a period of 1 week or longer following application of the topical patch NSAID formulation.

The Applicants submit that the combined teaching of the cited references fails to teach or suggest the above claim element.

In making the rejection, the Examiner cites Bockow as the primary reference teaching use of a topical composition containing a cyclooxygenase (COX) inhibitor for treating pain, but concedes that Bockow does not disclose the application of a topical NSAID patch formulation for treatment of the symptoms of carpal tunnel syndrome.

In attempting to provide the claim element cited above, the Examiner appears to rely on Edwards. Edwards is cited for teaching application of a topical banana peel extract formulation to the wrist of a subject in Example P, which is reproduced below for convenience.

EXAMPLE P

An individual suffering from carpal tunnel syndrome experienced soreness and swelling in her right arm. She also experienced numbness in her right hand. After she applied extract cream to her right wrist, the swelling and the pain subsided, and the feeling returned to her hand.

As evidenced above, nowhere does Edwards teach that application of the banana peel extract reduced symptoms of the individual for an **extended** period of time, i.e., 1 week or longer. Further, as Edwards provides no other data or teachings of treatment of carpal tunnel syndrome/median nerve pressure, Edwards fails to suggest

that application of the banana peel extract would ameliorate any of these symptoms for a period of 1 week or longer.

The Applicants have filed herewith the declaration of Dr. Larry Caldwell under 37 C.F.R. § 1.132 (hereinafter "the Declaration"), that provides evidence and statements demonstrating that the combined teaching of the cited references does not render the claimed method obvious. Specifically, in support of the contention that Edwards fails to teach or suggest the above claim element, the Declaration states, "nowhere in Example P does Edwards teach that the symptoms were ameliorated for an extended period of time, i.e., 1 week or longer. Just because Edwards' extract cream may give immediate relief of symptoms does not mean that the cream would work over an extended period of time, i.e., a period of 1 week or longer"

As such, neither Bockow nor Edwards teaches or suggests the amelioration of at least one symptom associated with median nerve pressure for a period of 1 week or longer, as claimed.

As Herbert is cited solely for use of oral NSAIDs in treatment of carpal tunnel syndrome; Hirano and Liebschutz are cited for teaching diclofenac patches; and the instant specification is cited for teaching a commercially available hydrogel adhesive patch; these references do not remedy the deficiency of Bockow and Edwards.

As such, the combined teaching of the cited references fails to teach or suggest each and every element of the claims and cannot render the claimed method obvious. Thus, the rejection may be withdrawn for this reason alone.

2) No predicted success in practicing the claimed invention

Furthermore, the Applicants submit that one of ordinary skill in the art would not have predicted success in practicing the claimed invention prior to the Applicants' work reported in the present application, as discussed in greater detail below.

The Declaration of Dr. Larry Caldwell provides evidence and statements of one of ordinary skill in the art to support the contention that one of ordinary skill in the art would not have predicted success in the claimed method – in particular, the amelioration of at least one symptom associated with pressure applied to the median nerve of the carpal tunnel of a host for a period of 1 week or longer following application of the topical patch NSAID formulation.

As described in the Declaration, "Prior to the actual reduction to practice reported in the application, it was not at all certain that application of a NSAID topical formulation would result in amelioration of at least one symptom associated with carpal tunnel syndrome/median nerve pressure, much less amelioration of the at least one symptom for a period of a week or longer." See the Declaration, item 5.

In attempting to establish this rejection, the Examiner appears to rely on Edwards' showing (Example P) of topical application of a banana peel extract to the wrist of a subject, as an asserted working exemplification that supports an anticipation of success in practicing the claimed method.

However, the Applicants submit that Edwards' cited example fails to support an anticipation of success in practicing the claimed method, for the reasons set forth below, as further evidenced by the Declaration of Dr. Larry Caldwell.

Edwards teaches that elemicin is a likely active agent of the banana peel extract (see Table 3 and col. 5, lines 59-62). Elemicin is a known psychoactive compound[1] that is partly responsible for the anticholinergic-like effects of raw nutmeg.[2] As such,

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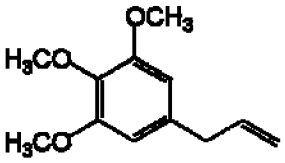
[1] Sangalli et al., "Toxicology of Nutmeg Abuse," Clinical Toxicology, 2000, Vol. 38, No. 6 , pages 671-678 ; Shulgin, Alexander T.; Sargent, Thornton W.; Naranjo, Claudio (1967). "Chemistry and psychopharmacology of nutmeg and of several related phenylisopropylamines". United States, Public Health Service Publication (1645): 202–214.

[2] McKenna A, Nordt SP, Ryan J (August 2004). "Acute nutmeg poisoning". European Journal of Emergency Medicine : Official Journal of the European Society for Emergency Medicine 11 (4): 240–1.

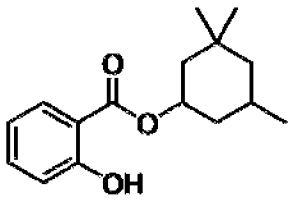
elemicin's mechanism of action is via blocking the neurotransmitter acetylcholine in the central and peripheral nervous system. For example, acetylcholine acts in the peripheral nervous system to activate muscles.

Edwards also identifies homosalate as an agent that may affect the activity of the extract. Homosalate is a common ingredient of lotions such as moisturizers and sunscreens because of its UV blocking properties (Edwards Example F), and is recently reported to have activity in vitro as an anti-androgen,[3] i.e., a **steroid** receptor antagonist.

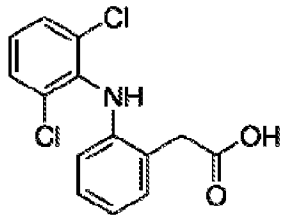
As such, the action of Edwards' banana peel extract appears based at best on the activities of elemicin and homosalate via the above described mechanisms of action.



Elemicin



Homosalate



Diclofenac

NSAIDs of the claimed method contain an acidic moiety that is important to the activity of the NSAID because it mimics the carboxylic acid of the native arachidonic acid substrate of COX enzymes.[4] See also instant specification, page 5, lines 8-11. A comparison of the structures of elemicin and homosalate with diclofenac shown above demonstrates that the agents of Edwards banana peel extract lack this feature of NSAIDs. As such, Edwards' agents are structurally distinct from NSAIDs of the claimed method because they lack the acidic feature important for NSAID-like activity, and "thus

[3] Ma et al., "UV Filters with Antagonistic Action at Androgen Receptors in the MDA-kb2 Cell Transcriptional-Activation Assay," Toxicol. Sci. (2003) 74 (1): 43-50

[4] Jack DeRuiter, "Non-steroidal anti-inflammatory drugs (NSAIDS)," Principles of Drug Action 2, Fall 2002, (www.duc.auburn.edu/~deruija/nsaids_2002.pdf)

could not act via the same mechanism of action as an NSAID." See the Declaration, item 3, page 2.

The Applicant's contention is further supported by the art described below. NSAIDs are a distinct class of non-narcotic (i.e., not psychoactive) anti-inflammatory drugs that inhibit prostaglandin synthesis via inhibition of cyclooxygenase (COX). NSAIDs' mechanism of action is to inhibit the activity of prostaglandins that act as messenger molecules in inflammation processes. As such, NSAIDs mechanism of action is clearly distinct from that of steroid opioid anti-inflammatory drugs which which are additive narcotics.[5]

However, Edwards' active agents have very different properties. As described above, elemicin is a psychoactive agent that blocks the neurotransmitter acetylcholine in the central and peripheral nervous systems. As such, elemicin has a completely different mechanism of action compared to an NSAID because it acts in the nervous system via blocking neurotransmitters rather than acting locally via inhibition of inflammation signaling pathways.

Furthermore, homosalate acts by mimicking the action of a steroid at a steroid receptor, i.e., as an anti-androgen, and as such, is clearly different from an **non-steroidal** NSAID. **Non-steroidal** anti-inflammatory drugs (NSAID) have been clearly distinguished from steroid-based anti-inflammatories and have different properties and mechanisms of action.[6]

As such, the active agents of the banana peel extract have distinct structures and completely different mechanisms of action compared to the NSAIDs of the claimed invention.

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[5] Nuutinen and Raj, "An overview of current and investigational non-narcotic drugs for treatment of acute and chronic pain" Current Pain and Headache Reports, Volume 2, Number 3, 187-192.

As established in the Declaration, "It is well known in the art that just because one particular topical formulation is administered to treat a condition does not mean that a different topical formulation containing a different active agent can also be effective in treating the condition. This is particularly true if the active agents have different mechanisms of action." Item 6b, page 6 of the Declaration.

Further, the Declaration states that "those skilled in the art would not extrapolate any results obtained with Edwards' extract to an NSAID transdermal formulation. " Item 6a, page 6 of the Declaration.

As such, prior to the reduction to practice reported in the current application, it was not at all certain that application of a NSAID topical formulation could be used to treat carpal tunnel syndrome/median nerve pressure. The Applicants are aware of no report prior to the priority date of the current application of the use of such a topical formulation to treat carpal tunnel syndrome.

One of ordinary skill in the art would not extrapolate the results obtained with Edwards' banana peel extract to an NSAID transdermal formulation because NSAID drugs have distinct structures from Edwards' active agents and act via a completely different mechanism of action. As such, Edwards provides insufficient support for a reasonable expectation of success for a method of topically applying a NSAID formulation to ameliorate at least one symptom associated with median nerve pressure, much less amelioration for 1 week or longer.

Furthermore, Herbert, Hirano, Liebschutz also fail to provide any support for a predicted success in practicing the claimed method.

Herbert merely discloses that oral NSAIDs, local steroidal drug injections, iontophoresis and ultrasound may be effective treatments for CTS. Nowhere does

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[6] Green, "Understanding NSAIDs: From aspirin to COX-2," Clinical Cornerstone, 3(5), 2001, 50-59

Herbert teach or suggest that application of a transdermal patch would be an effective treatment for CTS. Herbert's suggestion of oral NSAID treatment of CTS does not provide support for a predicted success in practicing the claimed method because "it is well known in the art that just because an active agent is administered orally to treat a medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition." See statement 6a and supporting references of the Galer Declaration filed November 21, 2006.

Neither Hirano nor Liebschutz provide a working exemplification of transdermal delivery in a host for treatment of any condition, much less treatment of any symptoms of CTS/median nerve pressure. Hirano and Liebschutz merely provide examples showing some *in vitro* permeation of hairless mouse skin or guinea pig skin. However, *In vitro* permeation through isolated mouse skin does not necessarily translate to transdermal delivery in a host[7] much less to amelioration of at a symptom associated with median nerve pressure for a period of 1 week or longer. As discussed above, one would not predict success without actually performing experiments and obtaining positive results.

Accordingly, one of ordinary skill in the art could not have predicted success in practicing the claimed invention prior to the Appellants' work reported in the present application because the teachings of cited references do not provide a reasonable expectation of success over the evidence provided by the Applicants.

In light of the above analysis, it is respectfully submitted that the Examiner has not established a *prima facie* case of obviousness because:

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[7] K. Walters, "Dermatological and transdermal formulations," in Drugs and the pharmaceutical sciences, Vol. 119, Marcel Dekker, New York, 2002, page 241, paragraphs 2 and 4.
"It is important to consider the ability of in vitro skin penetration techniques to predict skin permeation in vivo. Unless it can be demonstrated that in vitro skin penetration data is reasonable similar to absorption across skin in situ, there is little value in obtaining this data."
"Many such studies have been performed using small laboratory animals, and their relevance to human skin has always been questionable, especially in terms of risk assessment."

1) the combined teaching of the cited references does not teach or suggest the amelioration of at least one symptom associated with pressure applied to the median nerve of the carpal tunnel of a host for a period of 1 week or longer following application of the topical NSAID formulation; and

2) one of ordinary skill in the art could not have predicted success in practicing the claimed invention based on Edwards' insufficient support, since Edwards' banana peel extract includes active agents that have distinct structures and act via completely different mechanisms of action compared to an NSAID transdermal formulation.

Accordingly, Claims 1-2, 5-7, 10-11, 14-18, 24-30 and 32-40 are not obvious under 35 U.S.C. §103(a) over the cited references, and the Applicants respectfully request the rejection be withdrawn.

Claim 38

The Applicants submit that amended Claim 38 is further distinguished over the combined teaching of the cited references for specifying that at least one symptom associated with median nerve pressure is ameliorated for a period of 3 weeks or longer following application of a NSAID formulation.

As discussed above, nowhere does Edwards teach that the banana peel extract reduced symptoms in a subject over an extended period of time, much less for a period of 3 weeks or longer. As such, Edwards fails to teach or suggest the amelioration of at least one symptom for a period of 3 weeks or longer, as claimed.

Furthermore, for the same reasons set forth above, one of ordinary skill in the art would not extrapolate the results obtained with Edwards' banana peel extract to a NSAID formulation. One would not predict success in ameliorating at least one symptom associated with median nerve pressure after application of a NSAID formulation for any period of time, much less for a period of 3 weeks or longer, without actually performing experiments and obtaining positive results.

As such, Claim 38 is not obvious under 35 U.S.C. § 103(a) over the cited references because: 1) the combined teaching of the cited references does not teach or suggest amelioration of at least one symptom for 3 weeks or longer; and 2) one of ordinary skill in the art could not have predicted success in practicing the claimed method. Accordingly, the Applicants respectfully request the rejection of Claim 38 be withdrawn.

Claim 39

The Applicants submit that amended Claim 39 is further distinguished over the combined teaching of the cited references for specifying that at least one symptom associated with median nerve pressure is ameliorated for a period of several weeks or longer following application of a NSAID formulation.

As discussed above, nowhere does Edwards teach that the banana peel extract reduced a symptom in a subject over an extended period of time, much less for a period of several weeks or longer. As such, Edwards fails to teach or suggest the amelioration of at least one symptom for a period of several weeks or longer, as claimed.

Furthermore, for the same reasons set forth above, one of ordinary skill in the art would not extrapolate the results obtained with Edwards' banana peel extract to a NSAID formulation. One would not predict success in ameliorating at least one symptom associated with median nerve pressure after application of a NSAID formulation for any period of time, much less for a period of several weeks or longer, without actually performing experiments and obtaining positive results.

As such, Claim 39 is not obvious under 35 U.S.C. § 103(a) over the cited references because: 1) the combined teaching of the cited references does not teach or suggest amelioration of at least one symptom for several weeks or longer; and 2) one of ordinary skill in the art could not have predicted success in practicing the claimed method. Accordingly, the Applicants respectfully request the rejection of Claim 39 be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CALD-005.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: October 27, 2010 By: /Glenn J. Foulds, Reg. No. 64,714/
Glenn J. Foulds
Registration No. 64,714

Date: October 27, 2010 By: /Bret E. Field, Reg. No. 37,620/
Bret E. Field
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Enclosed: Declaration of L. Caldwell under 37 C.F.R. § 1.132

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